Novel Peripheral Kappa Opioid Product Candidates

Canaccord Healthcare

August, 2017

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Forward Looking Statements

This presentation contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. In some cases, you can identify forward-looking statements by the words “anticipate,” “believe,” “continue,” “estimate,” “expect,” “objective,” “ongoing,” “plan,” “propose,” “potential,” or “up-coming” and/or the negative of these terms, or other comparable terminology intended to identify statements about the future. Examples of these forward-looking statements in this presentation include, among other things, the expected timing of our other planned clinical trials; the potential results of ongoing and planned clinical trials; future regulatory and development milestones for the Company's product candidates; the size of the potential markets that are potentially addressable for the Company’s product candidates, including the postoperative and chronic pain markets, and the pruritus market; and the Company's expected cash reach.

These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain. Factors that may cause actual results to differ materially from any future results expressed or implied by any forward-looking statements include the risks described in the “Risk Factors” section of the Company’s Annual Report on Form 10-K for the year ended December 31, 2016, as well as those set forth from time to time in the Company’s other SEC filings, available at http://www.sec.gov. Any forward-looking statements speak only as of the date of this presentation.

The Company undertakes no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise except as required by law.

Cara: Developing First-in-Class Peripheral Opioid

- **Novel opioids designed to function without traditional opioid side effects**
  - Kappa opioid agonists with unique pharmacology and chemotype
  - NCEs with patent protection through at least 2027
  - MOA: Anti-Nociceptive(1)/Anti-Inflammatory & Anti-Pruritic

- **Three Ongoing Late-Stage Development Programs:**
  1. **Pruritus**
     - I.V. CR845 CKD-associated pruritus (CKD-aP) in hemodialysis (EoPII)
     - Oral CR845 – CKD-aP (Stage III-IV) and chronic liver disease-aP
  2. **Postoperative Pain**
     - Ongoing Phase 3 trial in abdominal surgery patients
  3. **Chronic Pain**
     - Phase 2b results: Reduction in worst joint pain score in hip OA patients

1. Blocking the detection of pain or injurious stimulus by sensory neurons

μ-Opioid Versus κ-Opioid Receptor Agonist Effects

	μ-opioid	κ-opioid
Central	• Respiratory depression • Analgesia • Nausea & vomiting • Euphoria • Addiction • Urinary retention • Miosis	• Hallucinations • Dysphoria • Diarrhea • Miosis
BBB		
Peripheral	• Constipation • Histamine release	• Analgesia • Anti-inflammatory • Anti-emetic • Anti-pruritic • Aquaresis

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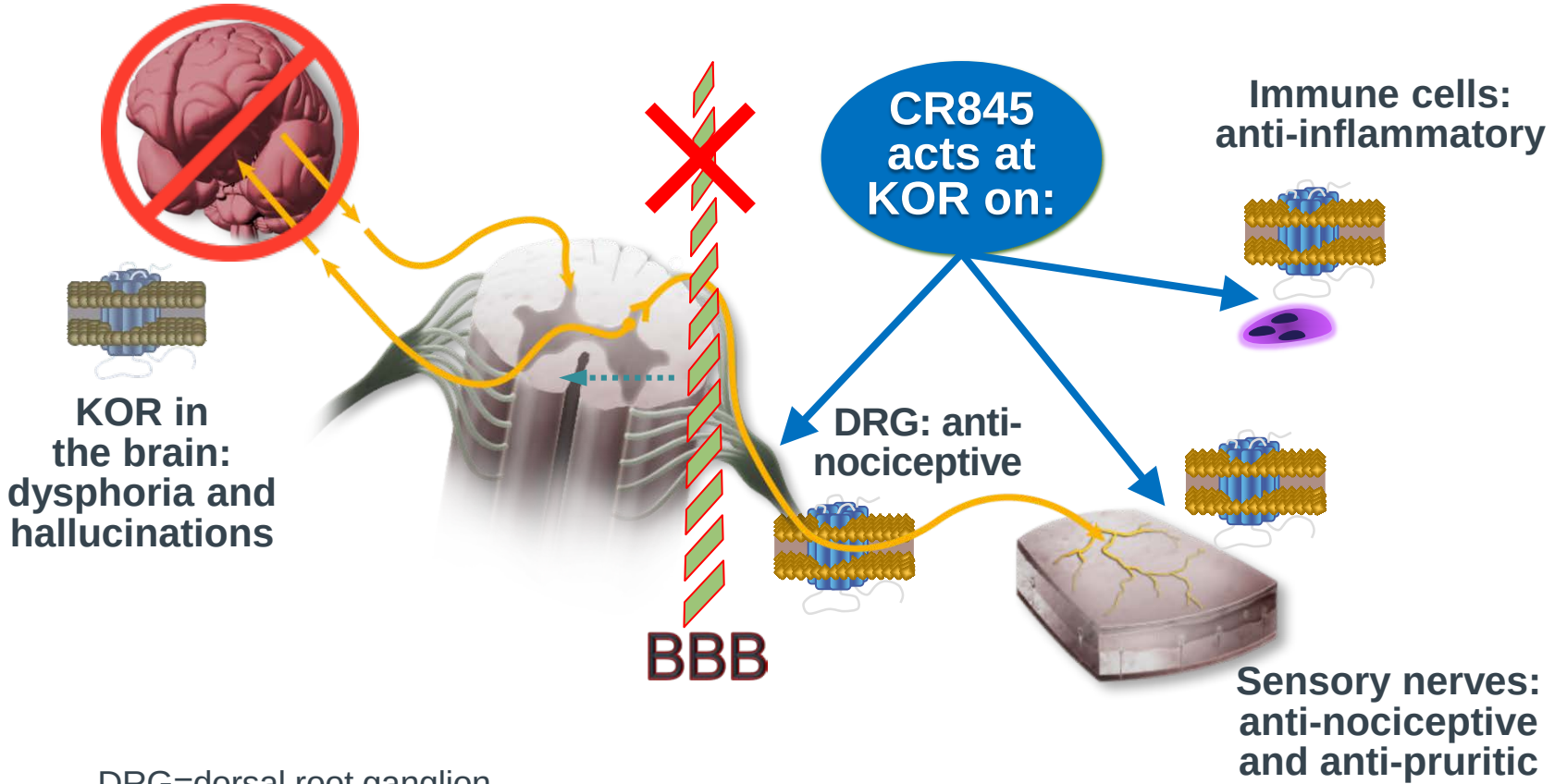
CR845 Effects Mediated by Peripheral κ-Opioid Receptors

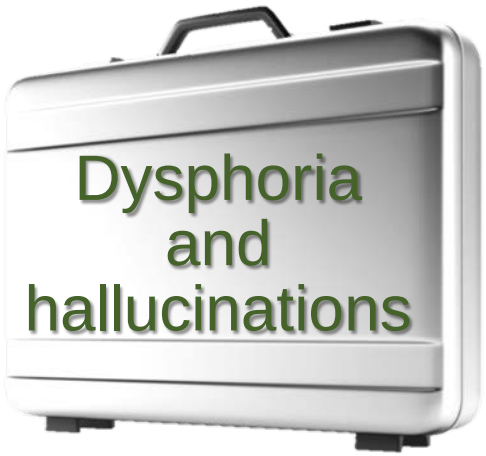
Novel Chemical Class – "hydrophilic" tetrapeptide



DRG=dorsal root ganglion

CR845: A Peripherally-Acting κ-Opioid Receptor Agonist

- Unique properties
  - ≥30,000-fold selectivity for κ-opioid receptors compared with μ- or δ-opioid receptors
  - Peptidic structure limits entry into CNS, potentially limiting:



  - Properties inherent to molecule
  - Not a formulation approach

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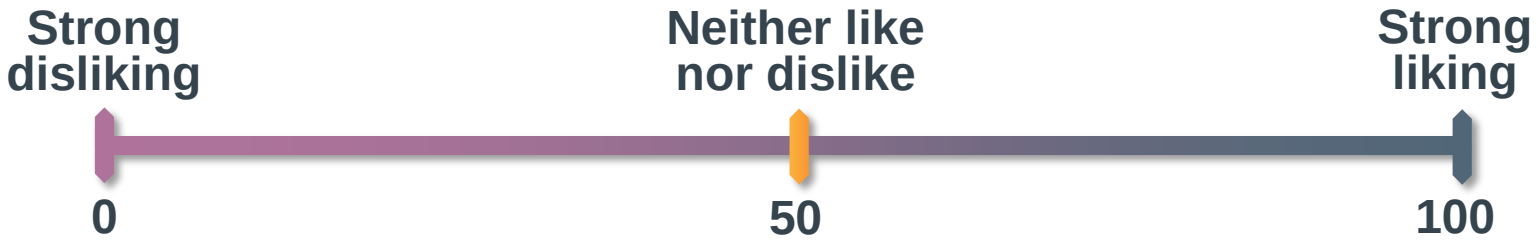
I.V. CR845
Human Abuse Liability Trial

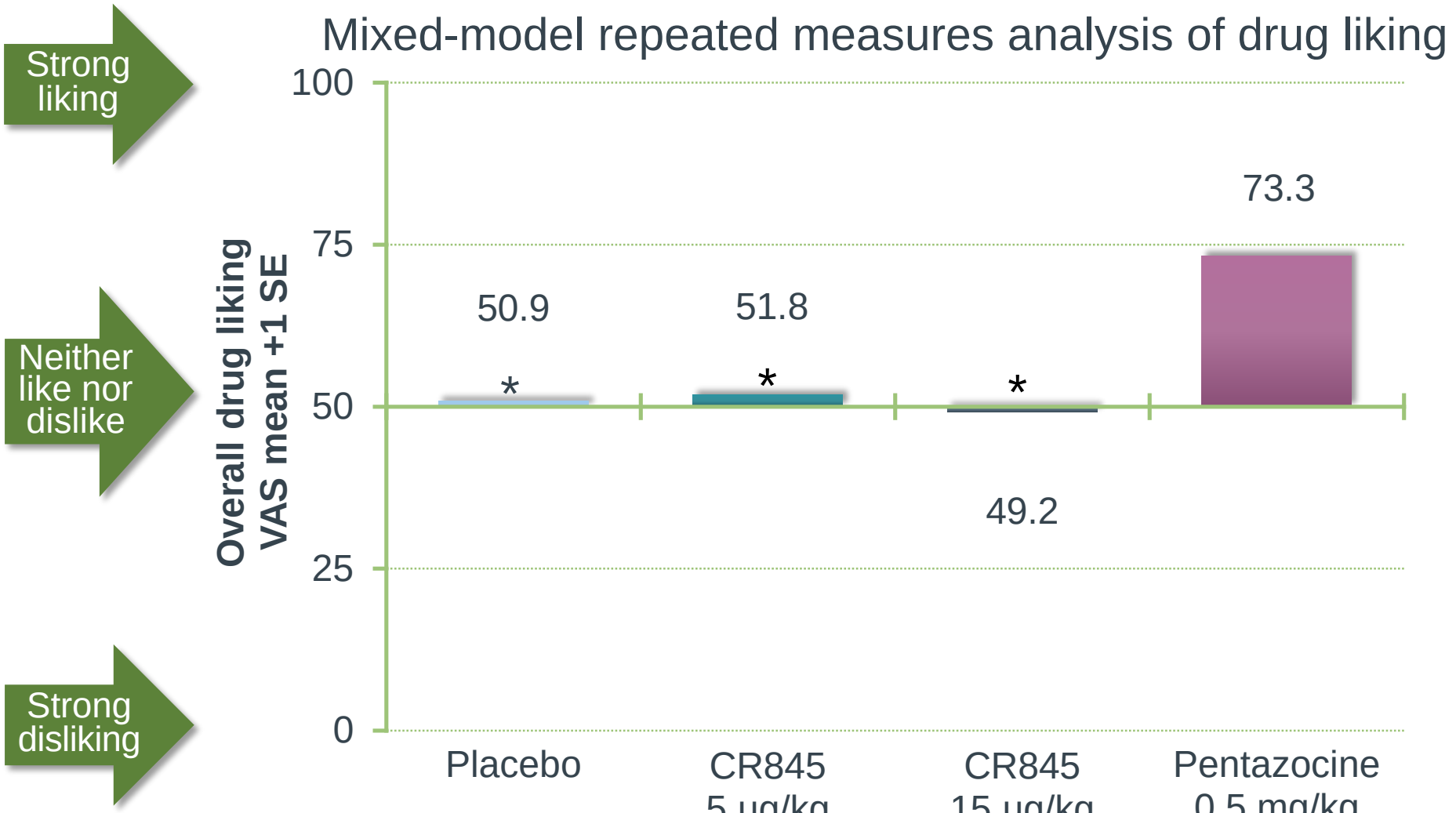
- Relative abuse potential vs. pentazocine* and placebo
- Non-dependent recreational opioid and hallucinogen users
- Study assessments with 3 bipolar visual analog scales (VAS)
  - Periodically from 5 minutes to 8 hours after dose:
    - *"Do you like the drug effect you are feeling now?"*



  - At 8 hours post dose:
    - *"Overall, my liking for this drug is: … "*
    - *"Would you want to take the drug you just received again,*

*A schedule IV opioid with κ activity

Human Abuse Liability Trial: CR845 Drug Liking Over 8-Hour Test Session



**p<0.001* Comparisons to pentazocine (Schedule IV)

CR845 Pipeline: Significant Progress in 1H, 2017

CLIN2101: I.V. CR845 – Uremic Pruritus

- Target 174 patients (Part A)
- 21 Sites Active
- ***Met primary and secondary endpoints in Itch and Quality of Life***

CLIN3001: I.V. CR845 – Acute Post-Op Pain

- Target 450 patients
- 23 Sites Active
- ***Full Enrollment: Q4, 2017***

CLIN2002: Oral CR845 – OA Chronic Pain

- Target 330 patients – expanded to 480
- 31 Sites Active
- ***Topline Data Q2: Hip OA patient response***

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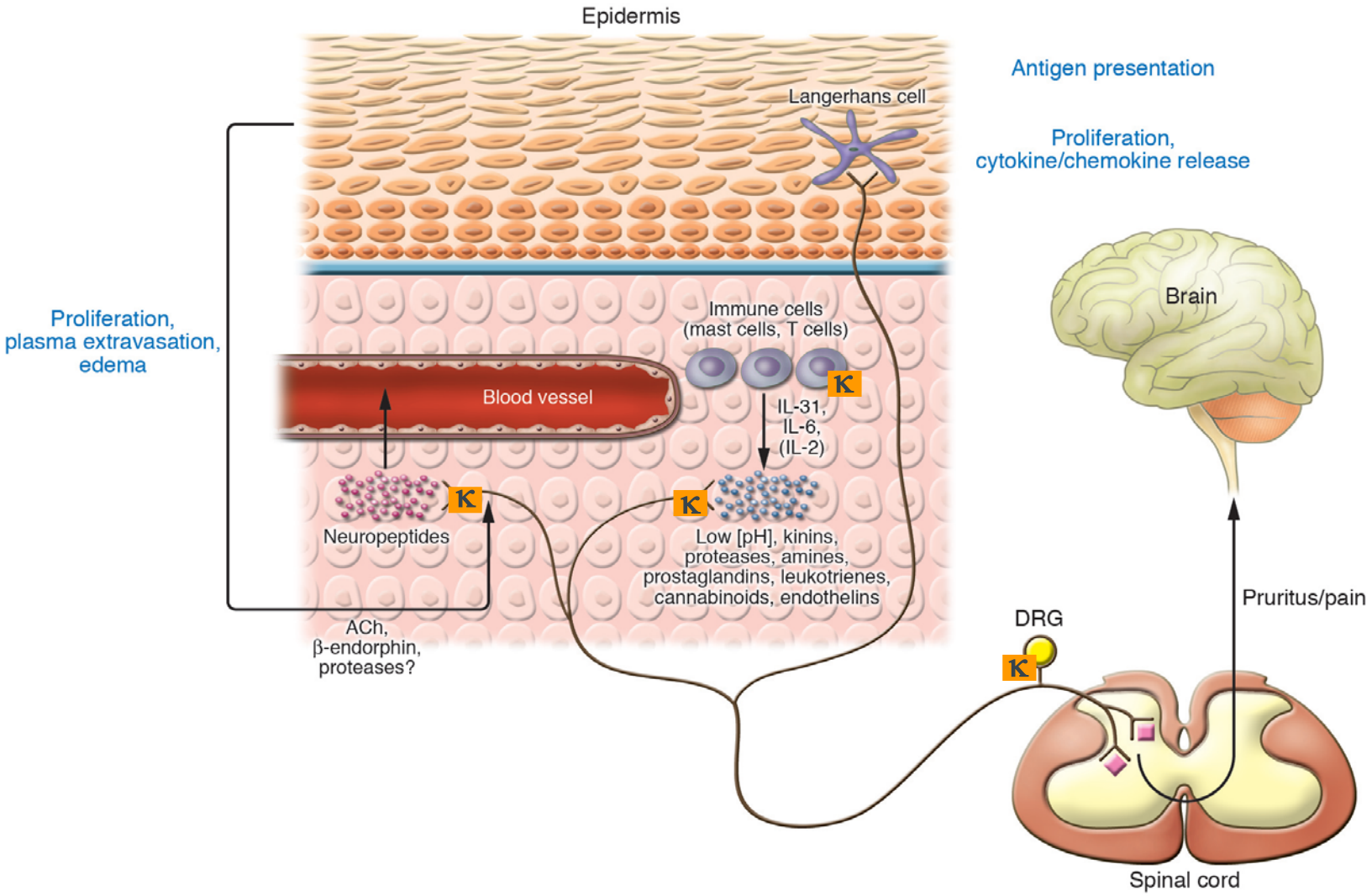
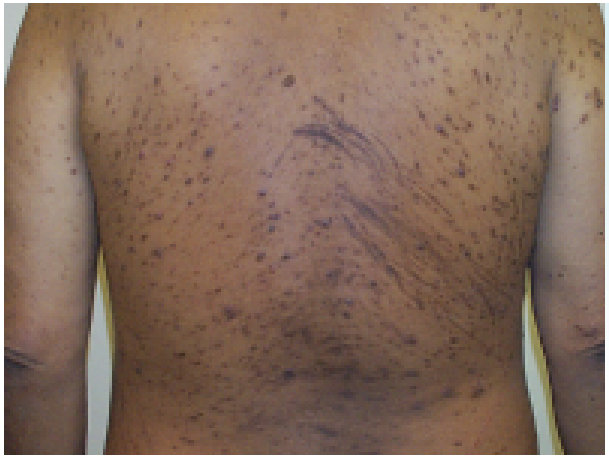
Pruritus And Pain – Common Pathway



Source: Paus et al.,J Clin Inv, 2006.

CKD-Associated Pruritus

- Severe, intractable itching experienced by CKD (Chronic Kidney Disease) patients
- Reduces quality of life and increases morality, cost and negative health outcomes
- Unresponsive to conventional itch medications: antihistamines, steroids



- *Most common on back, abdomen & arms*
- *Typically bilateral*
- *Excoriations in severe cases*

Patient Populations of CKD-Associated Pruritus: US

- Non-Dialysis
  - 12.2M patients diagnosed with CKD in US[1]
  - 32% of patients treated for pruritus[1]
  - Potential patient population of 4.0M
- Dialysis
  - 456K patients on dialysis in US[2]
  - 60-70% of patients with pruritus[3,4]
  - Potential patient population of 200-300 K

1. IMS Health, Pruritus Market Landscape Analysis, October 2014
2. ESRD Patients in 2013 - A Global Perspective. Fresenius Medical Care. 2014.
3. Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant.* 2006;21:3495-3505.
4. Ramakrishnan et al. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. *International Journal of Nephrology and Renovascular Disease.* 2014:7 1–12

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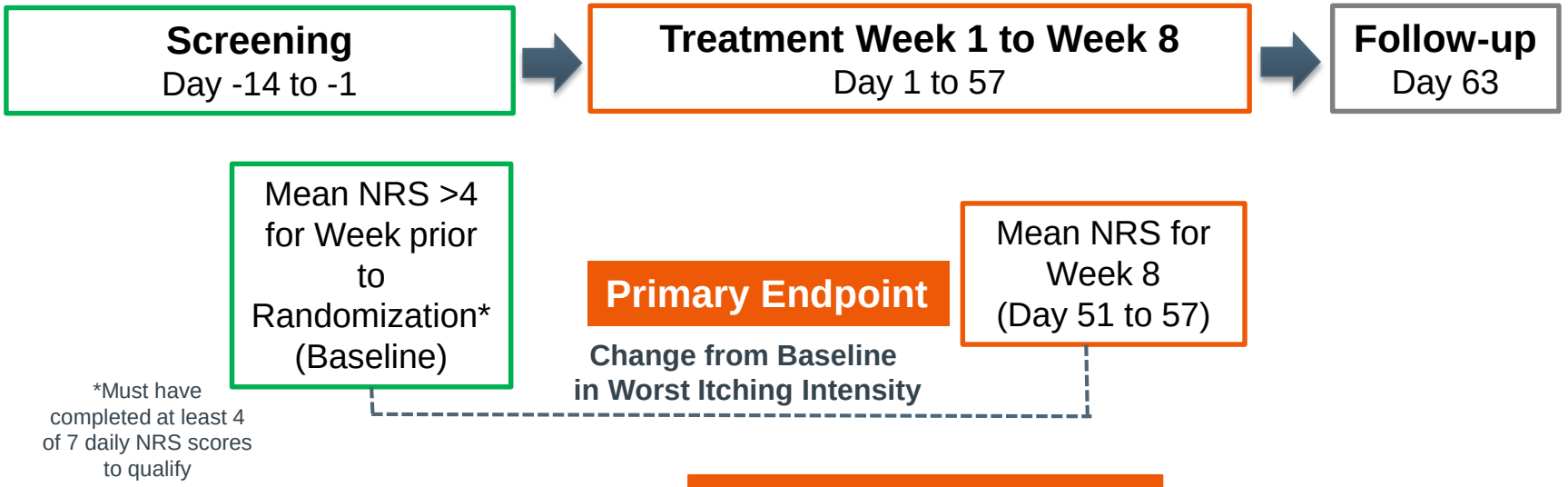
CR845-CLIN2101-A
Study Design

- Randomized, Double-Blind, Placebo-Controlled Study in Hemodialysis Patients with Moderate-to Severe Pruritus
- Doses of IV CR845 evaluated: 0.5, 1.0 and 1.5 mcg/kg
- 8-week treatment period
  - Dosing after each dialysis (3 times per week)
- Multi-center:
  - 33 U.S. sites
  - 174 patients randomized
    - Placebo: 45
    - CR845: 129

CR845-CLIN2101- A
Study Design Schematic and Patient-Reported Outcomes



Secondary/Exploratory Endpoints

Change from Baseline in QOL

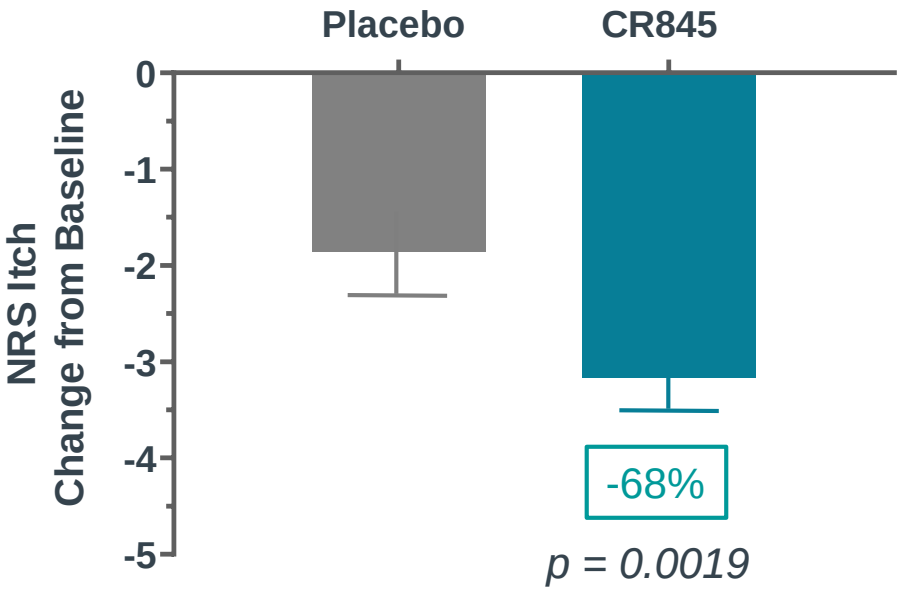
Predose (Baseline=Day 1)	**Week 8 (Day 57)**

- **Skindex-10**
- 5-D Itch Scale (multidimensional)
- Sleep disturbance subscale (MOS)
- Patient Global Impression of Change
- Patient Global impression of Worst itch Severity

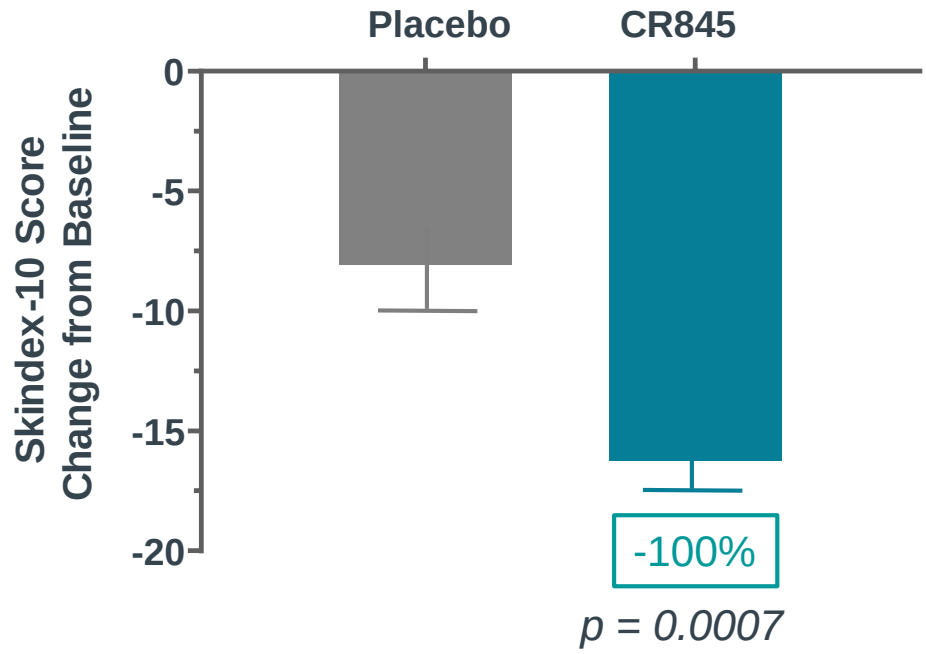
CR845-CLIN2101-A
Primary and Secondary Endpoints

Demonstrated efficacy in reduction of itch (NRS) and improvement in Quality of Life (Skindex-10) at end of the 8 week treatment period

Worst Itch Intensity



Quality of Life



Pearson's Correlation of the Worst Itching Intensity NRS with Skindex-10: r=0.67, p<0.0001

LS Mean ± SEM
Full Analysis Population

Full Analysis Population: all randomized patients who received at least 1 dose of double-blind study drug.

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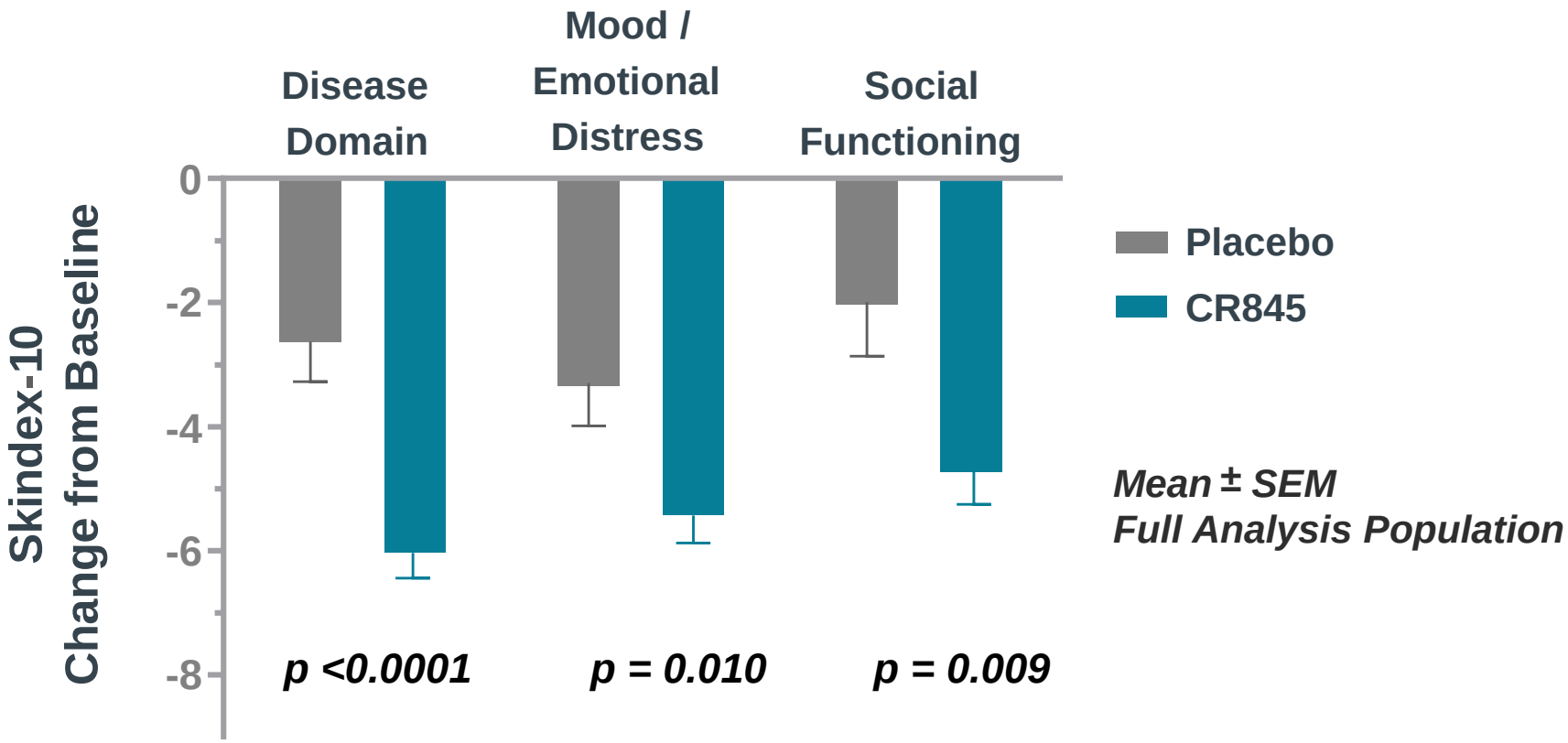
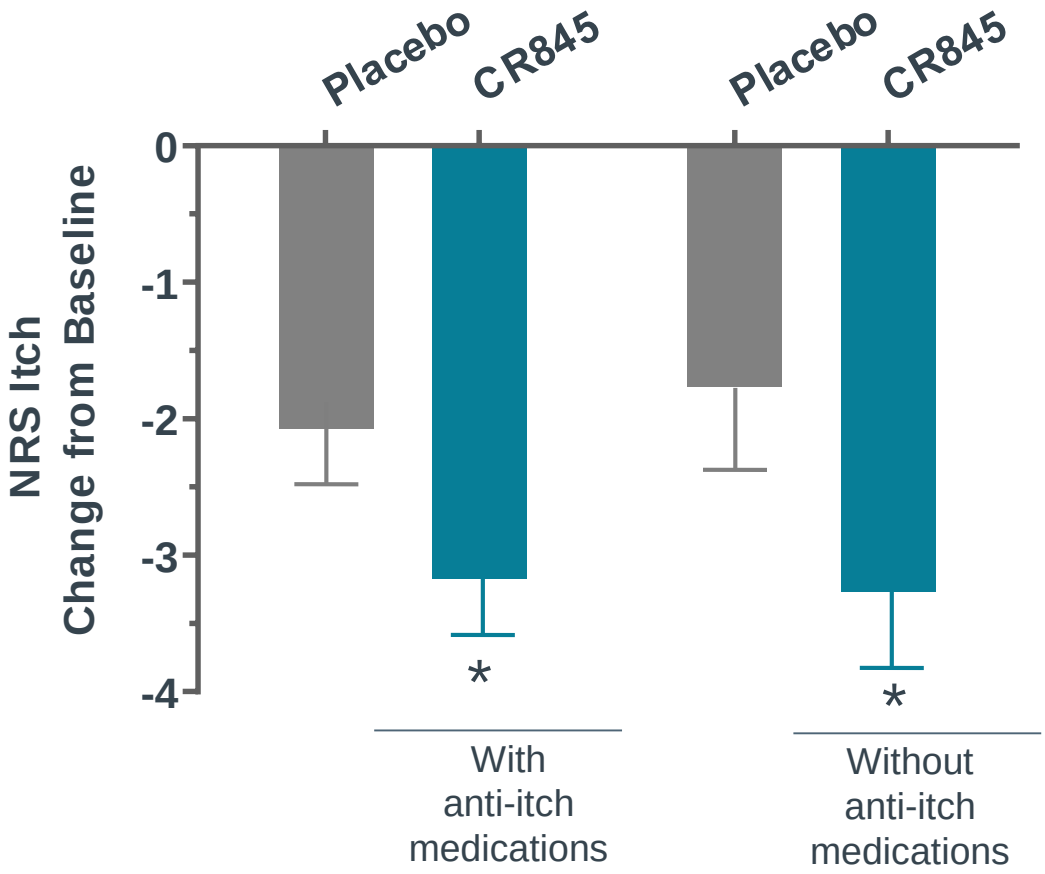
CR845 Improved Quality of Life (Skindex-10) Measures



CR845-treated Patients Exhibited Statistically Significant Improvement Across All QoL Domains

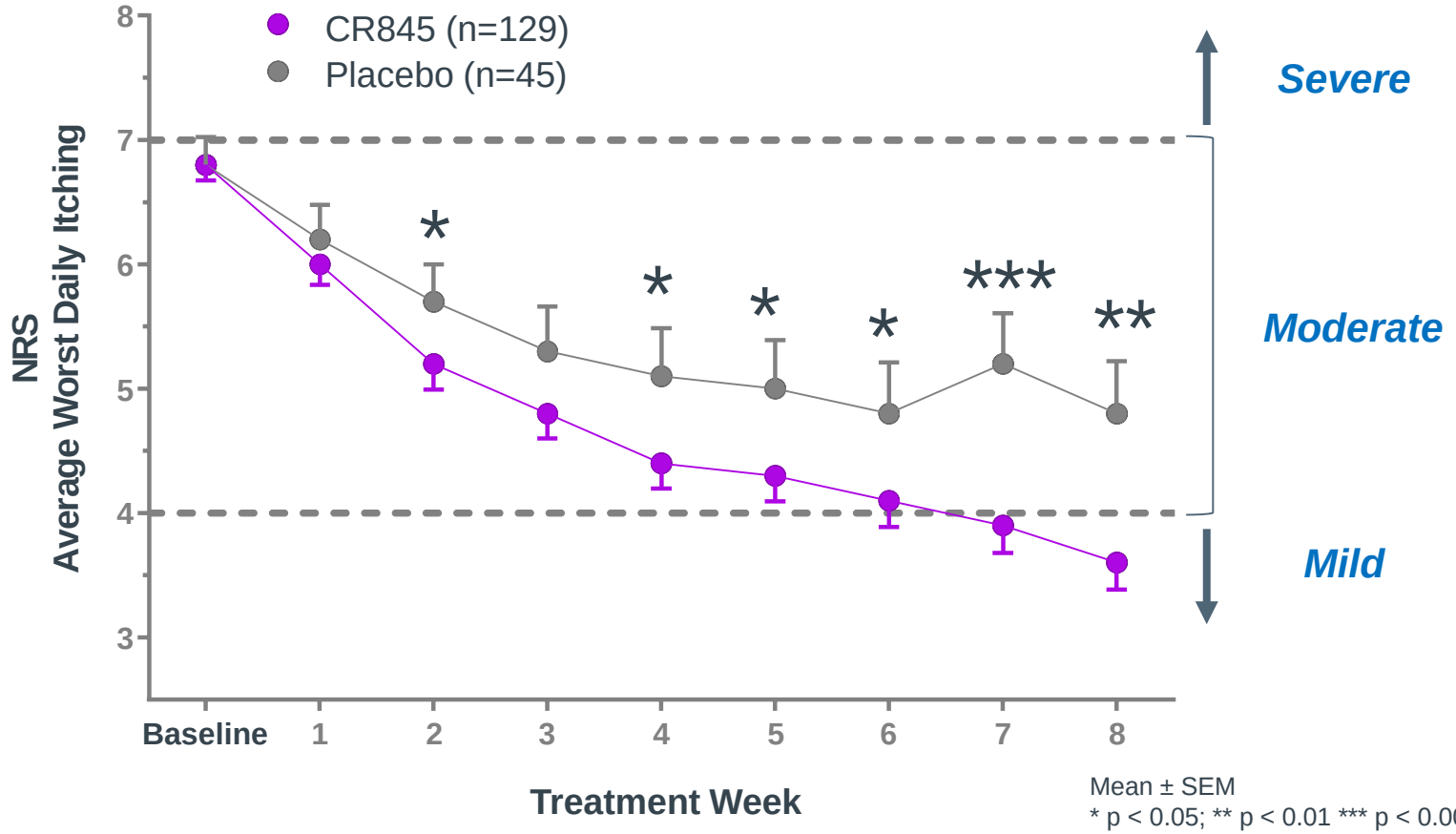
Baseline defined as assessments collected on Day 1 prior to first dose

Change in NRS Worst Itch Intensity Not Different Based on Prior Use of Anti-Itch Medications



- 42% of all patients reported prior use of anti-itch medication and were stratified prior to randomization
- Anti-itch medications included primarily antihistamines and corticosteroids

Time Course - Worst Itching Score (NRS)



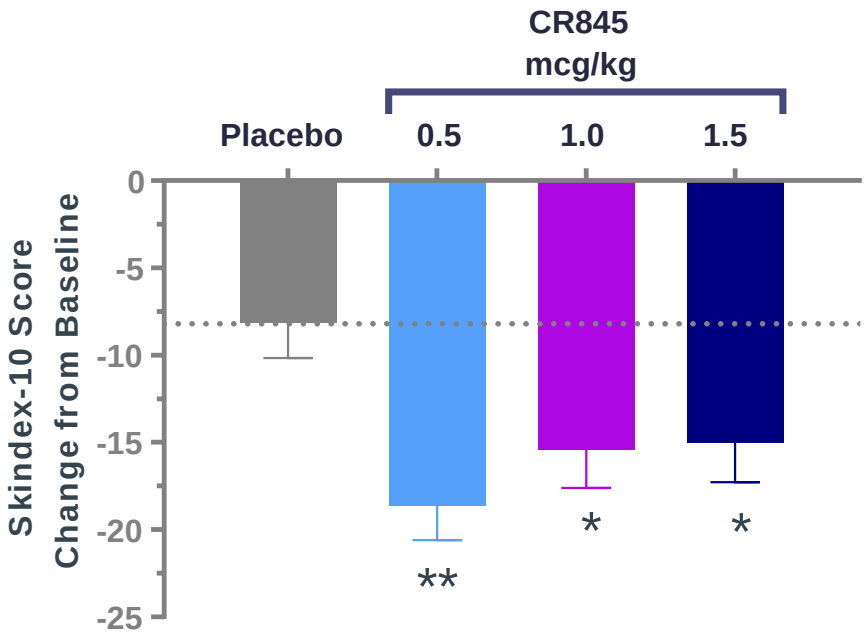
Mean ± SEM
* p < 0.05; ** p < 0.01 *** p < 0.001 vs Placebo

- Reduction of Worst itch intensity begins on Week 1 and continues to improve through Week 8.
  - Patients on placebo show initial improvement that plateaus

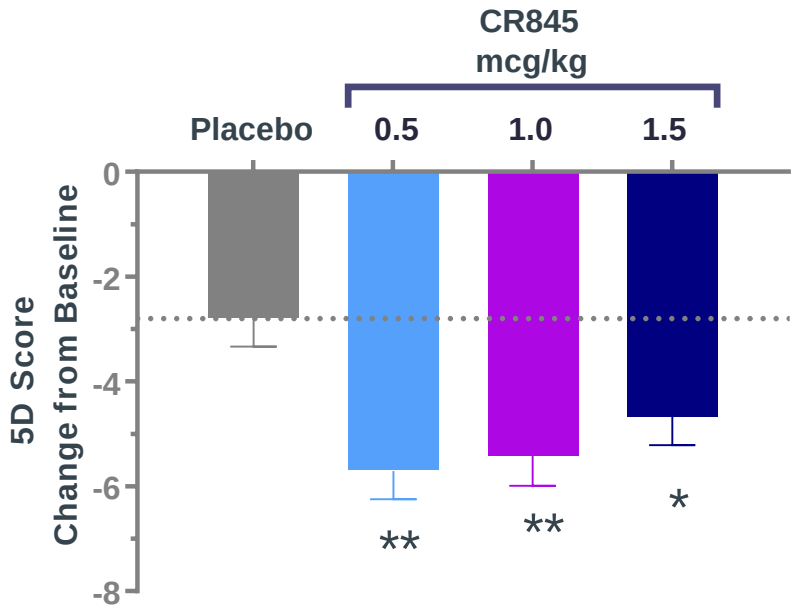
Severity Bands based on Reich et al, Acta Derm Venereol 2012

Improvement in Quality-of-Life Measures Across All Dose Groups

Skindex-10



5-D Itch



LS Mean ± SEM
* p <0.05, ** P<0.001 vs Placebo

Pearson's Correlations of the Worst Itching Intensity NRS and Skindex-10 with 5-D Itch: r=0.71 and r=0.74, respectively; p<0.0001

The 5-D Itch scale covers 5 domains: duration of itch/day, degree, direction (improvement/worse), disability (sleep, social, housework/errands, work/school), distribution (parts of the body)

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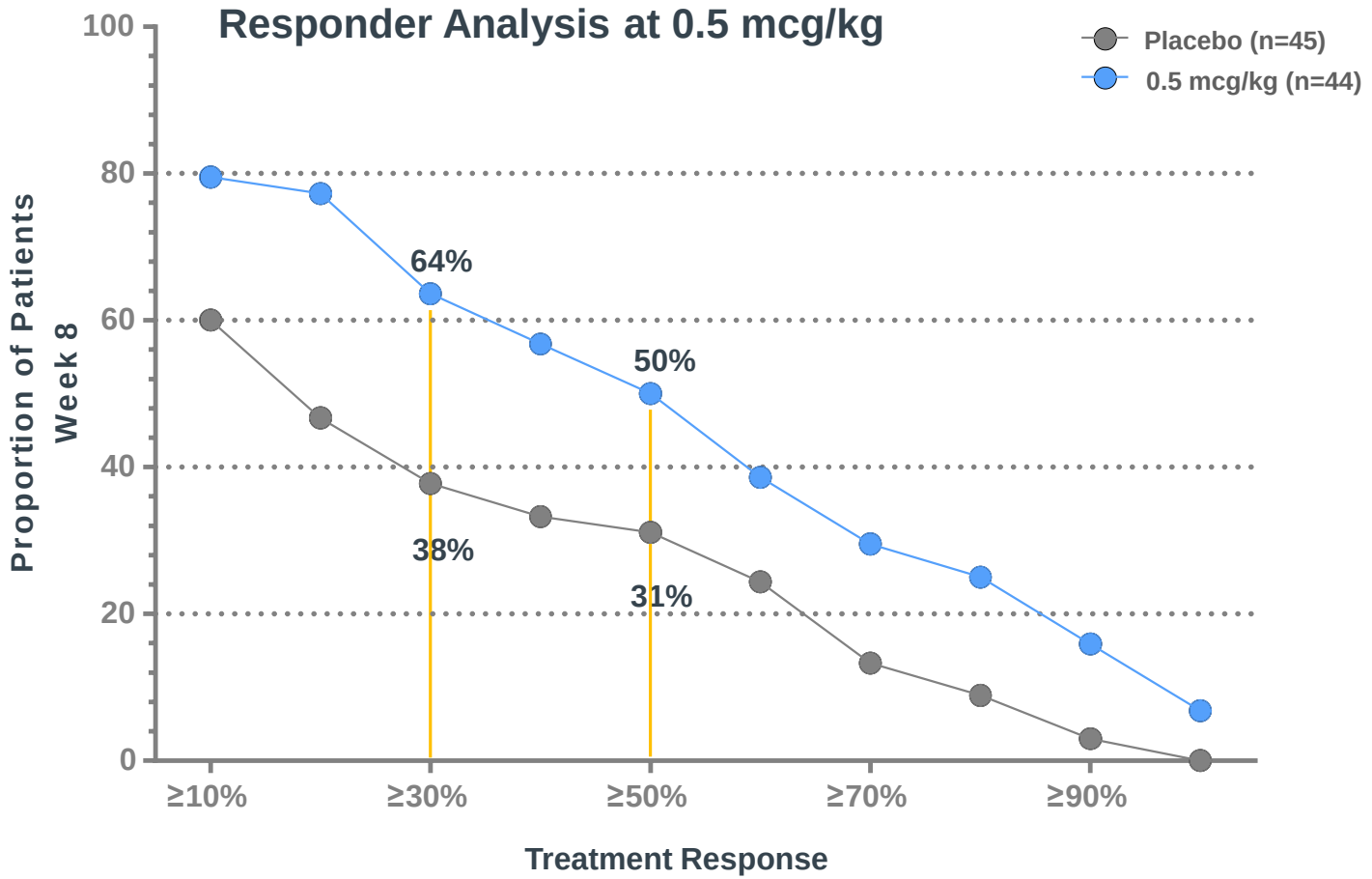
CR845: Demonstrated Clinically Meaningful Change in Worst Itching Intensity



Change of ≥ 2 points on the Worst Itching Intensity NRS represents a clinically meaningful improvement in NRS scores (results based on distribution- and anchor-based methods, taking into account all of the results for the CR845-CLIN2101 study, i.e., primary, secondary, and exploratory endpoints)

CLIN2101-A: Summary

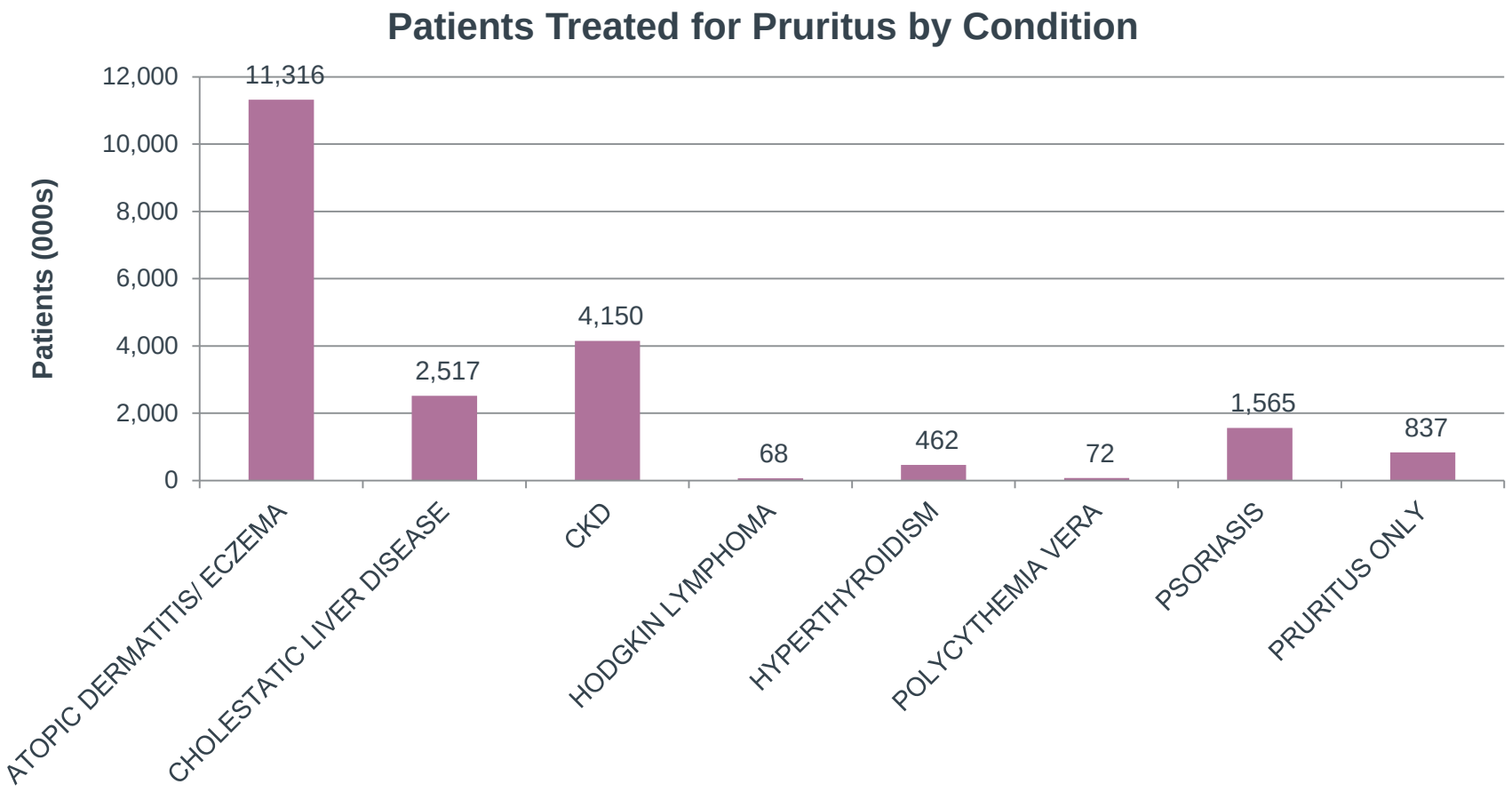
- Met primary and secondary endpoints
  - reduction in itch intensity and improvement of quality of life measures
- Validated sustained treatment benefit over 2 months across multiple measures
- Clinically meaningful effect (responder analysis)
- Clinically meaningful reduction in itch intensity confirmed with statistically significant improvement across multiple Quality-of-Life measures for the 0.5 mcg/kg dose group and with all CR845 dose groups combined:
  - 5-D Itch Scale
  - Sleep disturbance subscale (MOS)
  - Patient Global Impression of Change
  - Patient Global impression of Worst itch Severity
- **Designated Breakthrough Therapy by FDA in Q2, 2017**

Next Steps: I.V. CR845 Initiation Phase 3 Program

- Initiation open-label long-term safety extension trial (2Q2017)
  - 0.5 mcg/kg CR845 dose administered at end of each dialysis for up to 52 weeks
  - Patients who previously participated in the Phase 2 studies CR845-CLIN2005-B and CLIN2101-A
- End-of-Phase 2 meeting (3Q2017)
- Initiate Pivotal Phase 3 trial (4Q2017)

Patients Treated for Pruritus by Diagnosis United States - 2013

Among patients with conditions treated for pruritus, Atopic Dermatitis/Eczema, CKD and CLD are the largest populations



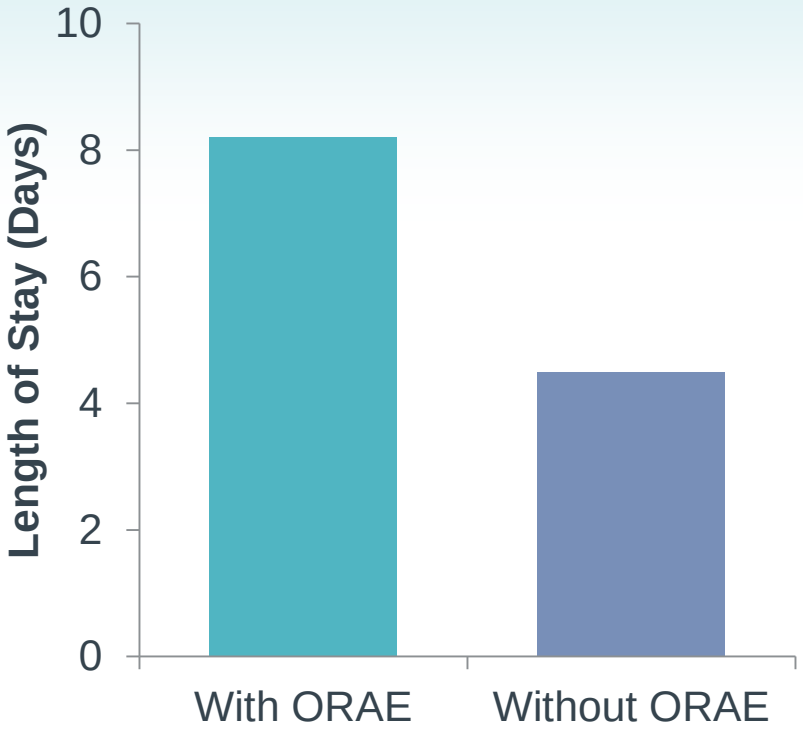
Clinical Needs In Post-Op Pain

Unmet Market Needs

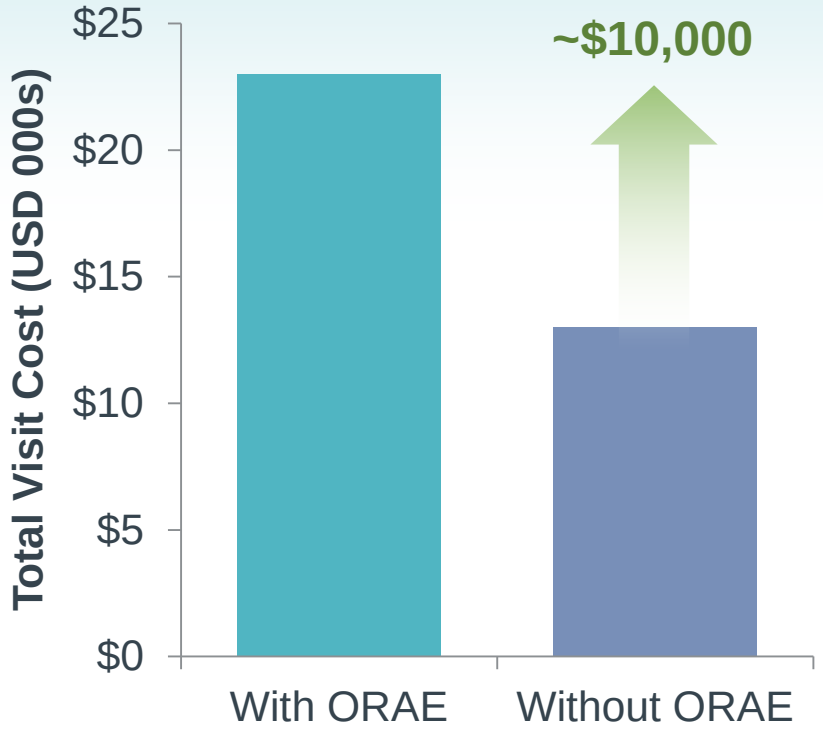
- Multimodal analgesia (ASA and ERAS)
  - Different MOAs to maximize analgesia
  - Anti-inflammatory benefits vs. mu opioids
- Reduction in mu opioid usage and side effects
  - Respiratory Depression
  - Nausea / Vomiting
  - Abuse Liability
- Results in better patient outcomes, decreased length of stay and reduction in overall health care costs

Surgical Database Research: Opioid-Related AEs Significantly Increase Length of Hospital Stay and Costs

Mean Length of Stay



Mean Total Visit Cost



Source: T. J. Gan et. al. *"Opioid-Related Adverse Events Increase the Length Of Stay and Drive Up Total Cost of Care in A National Database of Post-Surgical Patients"*; International Anesthesia Research Society Meeting, 2012 (unmatched means based on 324,568 patients; $p < 0.0001$).

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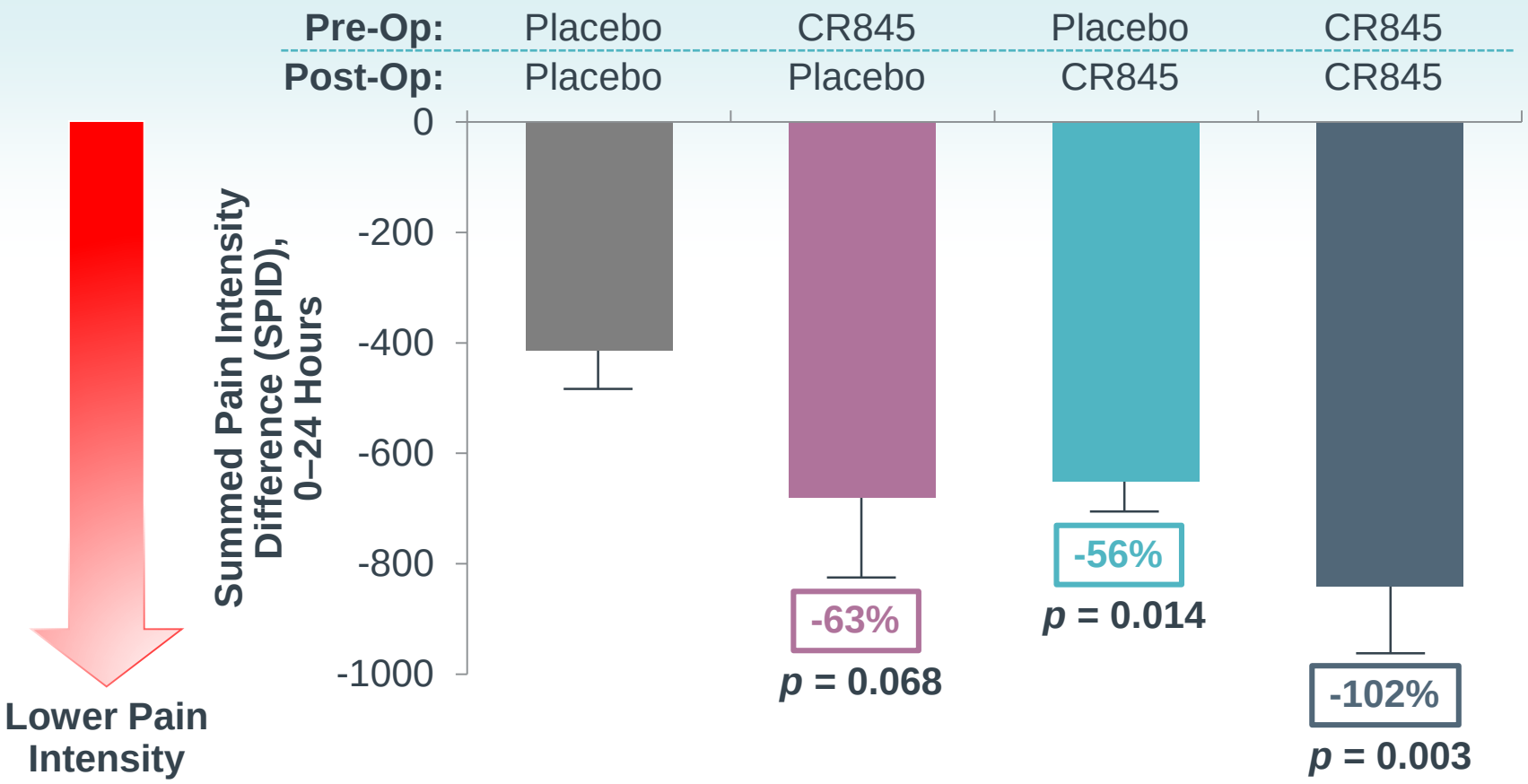
CR845 Phase 2 Hysterectomy Study: Significantly Reduced Post-Op Pain

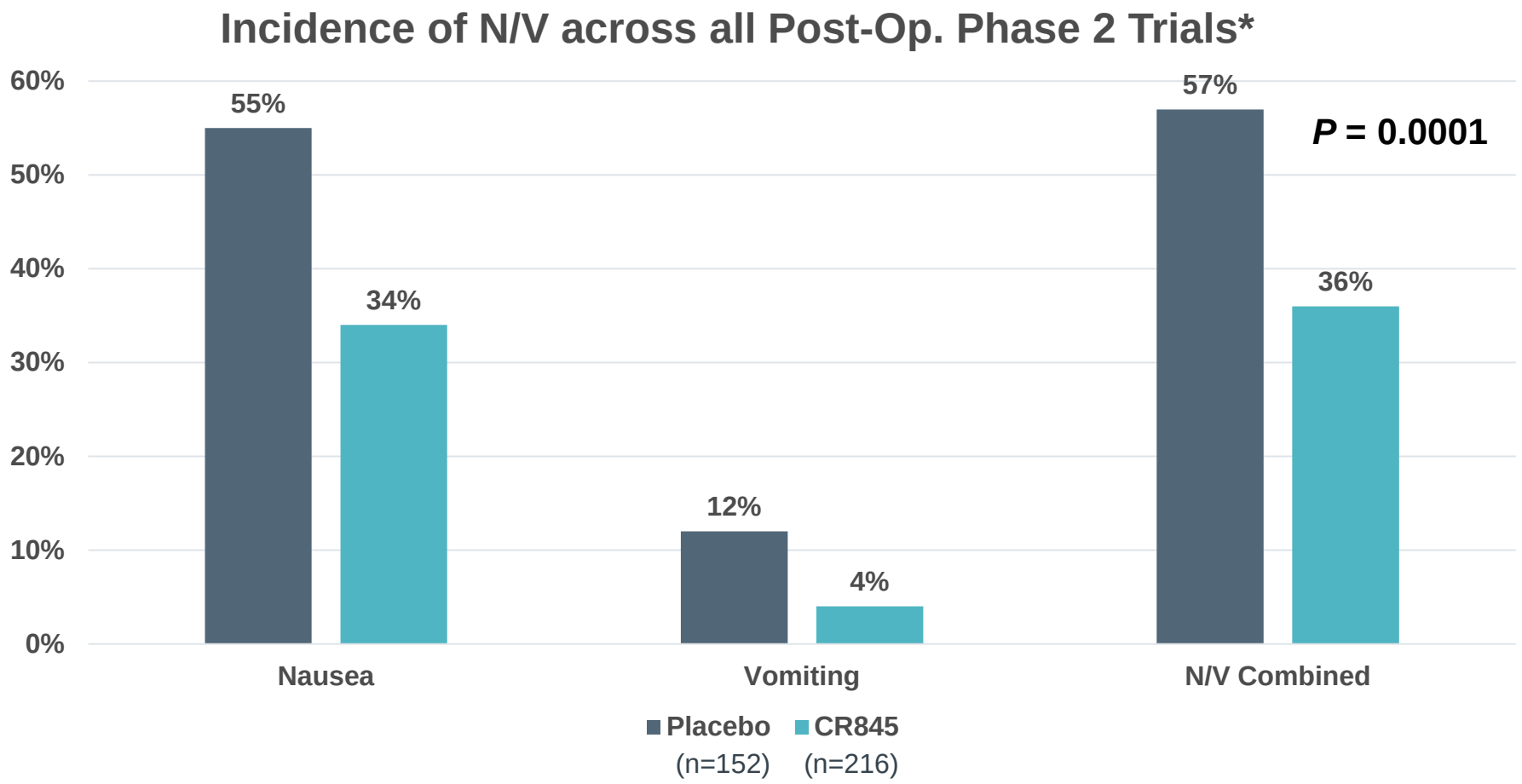
CLIN2002 Trial

Primary FDA Endpoint Met for Acute Pain



$SPID_{0-24}$ (mITT), Mean ± SEM. N = 71, 19, 71 and 20, respectively.

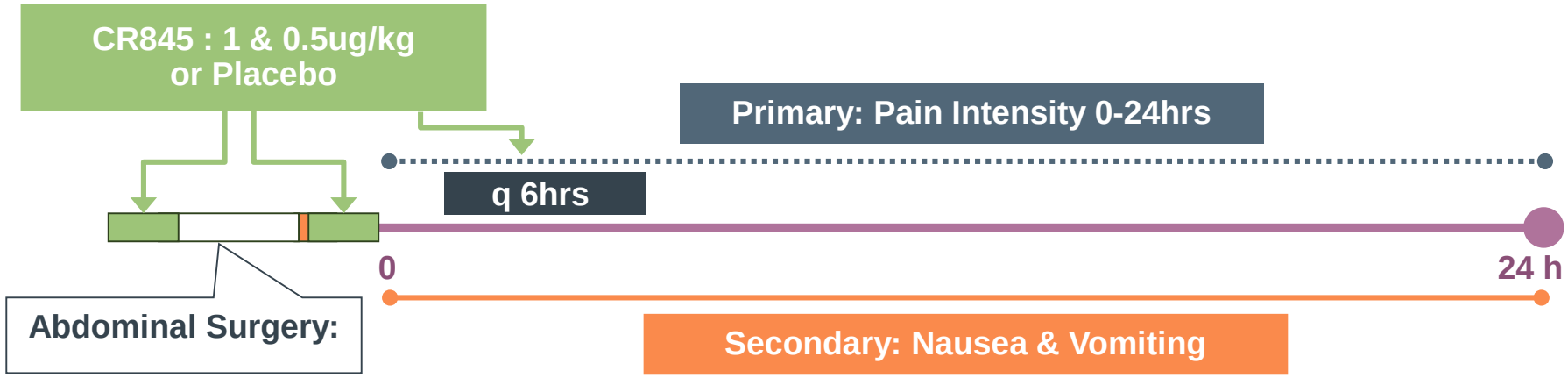
CR845 Provided Post-operative Analgesia and Reduced Post-operative Nausea and Vomiting



* Three Phase 2 post-operative pain studies: CLIN2001 (laparoscopic hysterectomy), CLIN2002 (laparoscopic hysterectomy), CLIN2003 (bunionectomy)

Ongoing CLIN3001 Post-Op Pain Adaptive Phase 3 Abdominal Surgeries: Pre- and Post-Surgical Treatment

CLIN3001 Trial



- Multi-center: 25 U.S. hospital sites, max. 450 patients
- Randomized, double-blind
- Endpoints:
  - Pain intensity 0-24hrs
  - Nausea & Vomiting
  - Rescue medication used (IV morphine)
  - Global evaluation of medication

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Osteoarthritis Phase 2b Trial CLIN2002 Protocol Overview

Main Study Objective

- Efficacy of oral CR845 in patients with osteoarthritis (OA) of the hip or knee
- Safety and tolerability over 8 week period in patients

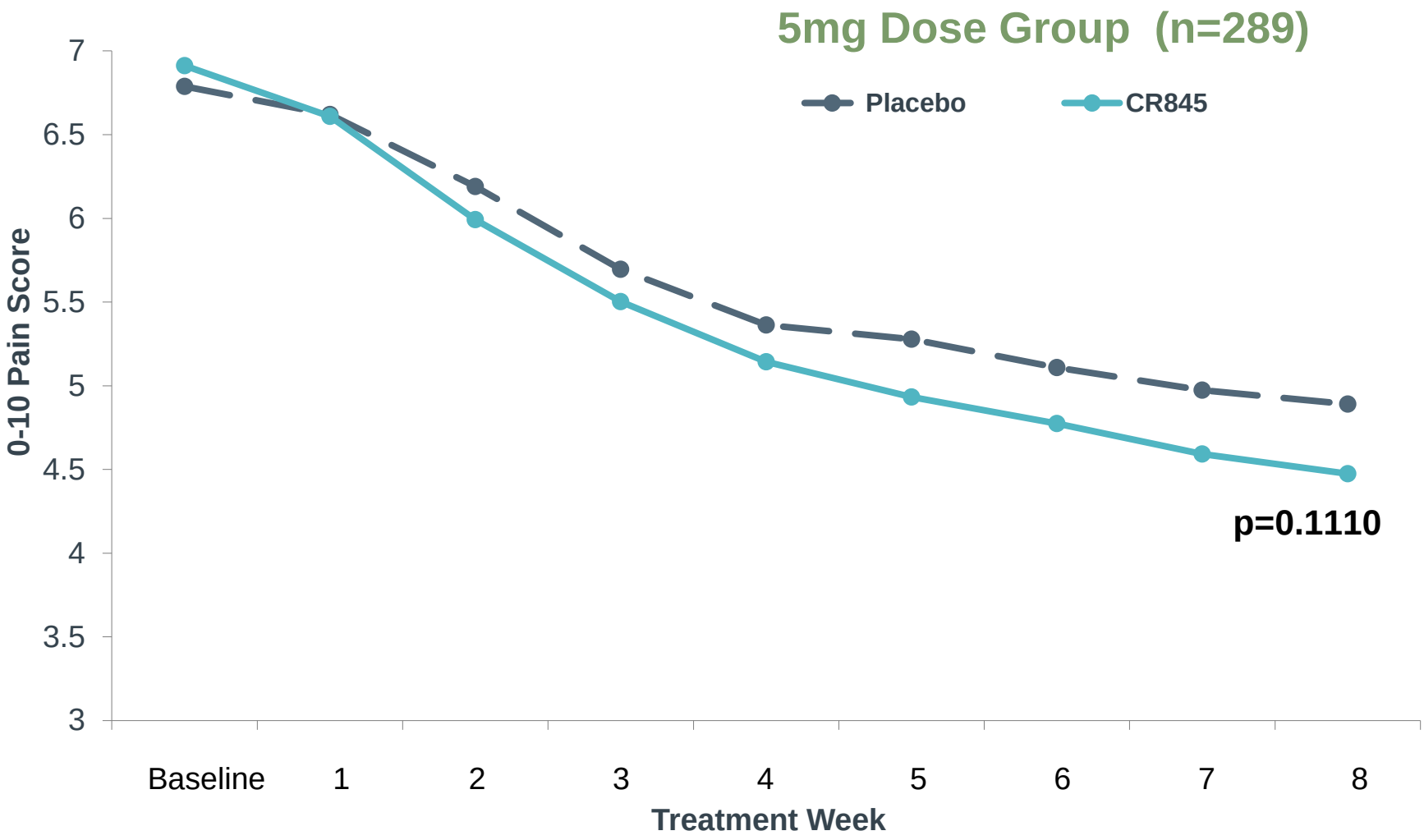
Study Design

- Double-blind, placebo-controlled study with twice daily (b.i.d.) doses of oral CR845 over an eight week treatment period in patients with moderate-to-severe pain (≥ 5) associated with OA.
  - Four week titration period for a response (tablet strengths 1mg, 2.5mg & 5mg).
  - Four week maintenance period on dose with response.

Patients

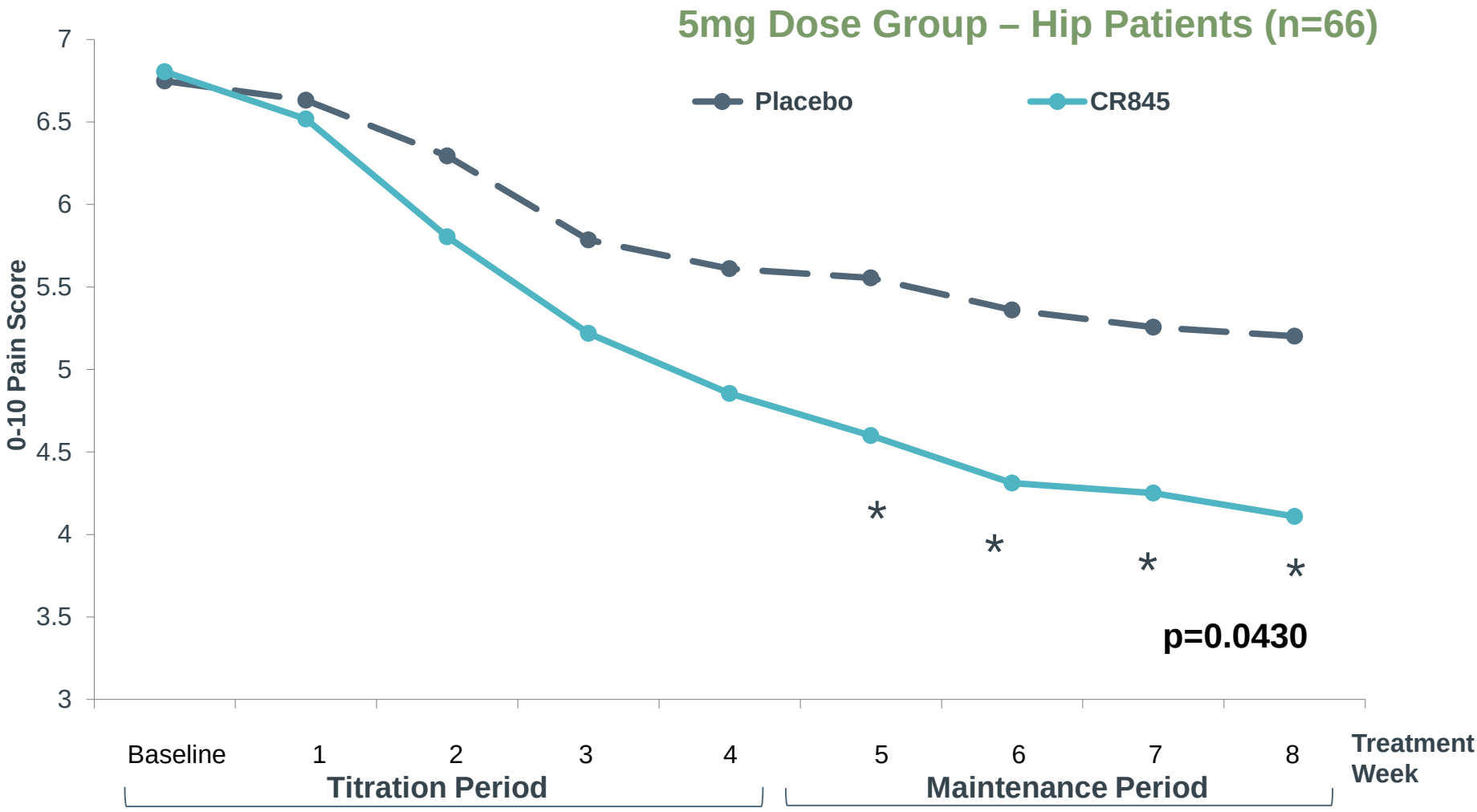
- 476 male and female patients – 33 U.S. sites

Mean Weekly NRS Pain Score – All Patients



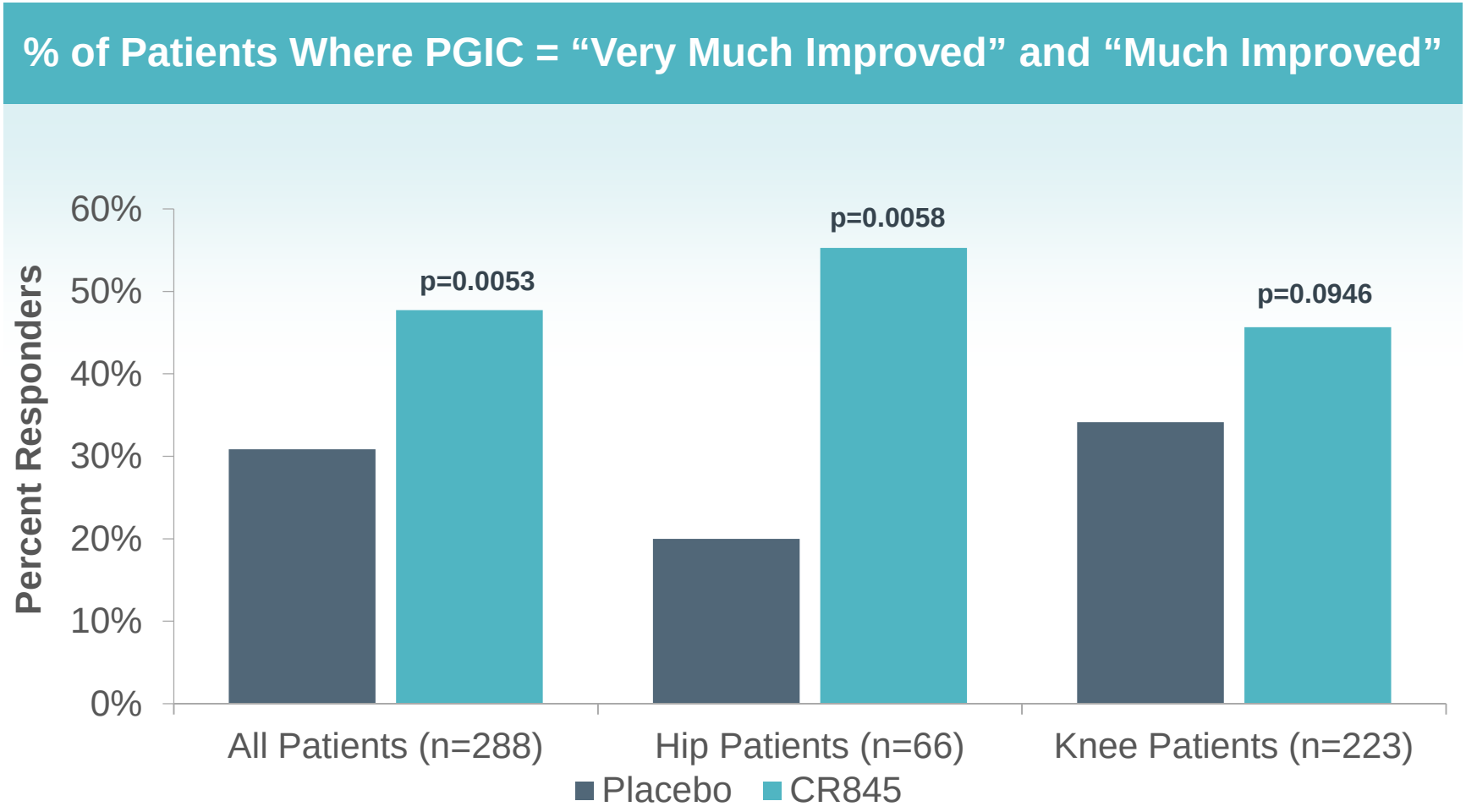
LS Means from MMRM with treatment, week, treatment by week interaction as terms in the model, baseline pain and strata as covariates, and subject as a random effect

Mean Weekly NRS Pain Score – Hip Patients



LS Means from MMRM with treatment, week, treatment by week interaction as terms in the model, baseline pain as a covariate, and subject as a random effect

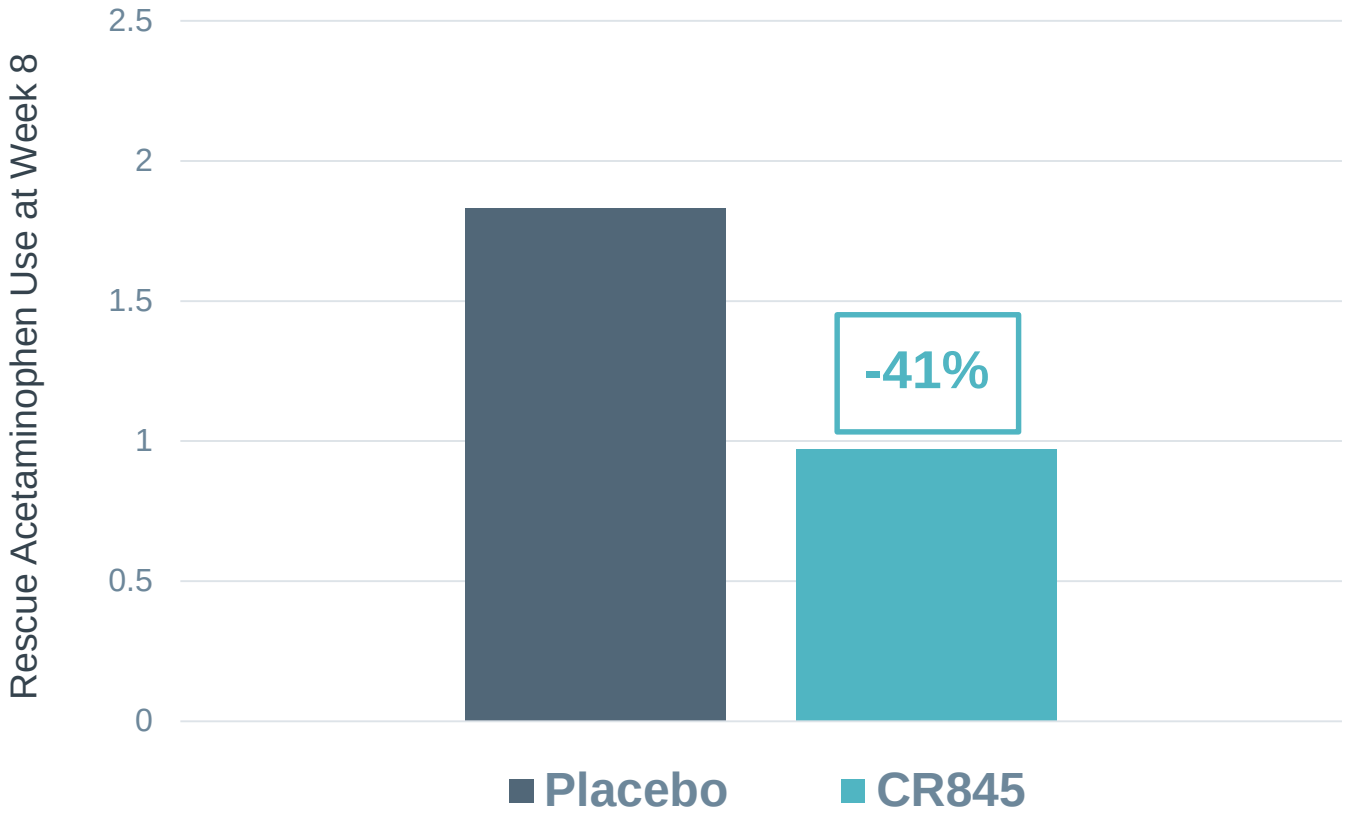
CLIN2002 PGIC Responders – 5mg Dose Group



(Cochran-Mantel-Haenszel test, 2-sided).

CLIN2002 Acetaminophen Use at Week 8

5mg Dose Group – Hip Patients (n=66)



67% of CR845 vs 43% of Placebo Patients Did Not Require Any Rescue Medication, Week 8

CLIN2002 Comparison of Adverse Events ≥ 5%

Adverse Event	Placebo	CR845	[a]OxyContin- IR	[b]Duloxetine
Constipation	1.9%	13.3%	23-26%	10%
Dizziness	1.9%	8.2%	13-16%	9%
Dry mouth	1.9%	5.7%	6-7%	11%

a. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020553s059lbl.pdf
b. http://pi.lilly.com/us/cymbalta-pi.pdf

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Comparative Efficacy in NRS Pain in OA Studies

Drug	Time	Change from BL	% Change from BL
Naproxen[1]	2 weeks	-2.5	35%
Celecoxib[1]	2 weeks	-2.5	35%
Duloxetine[2] (30mg/day)	2 weeks	-1.6	26%
Oxycodone CR[3]	12 weeks	-1.7	26%
CR845 (5mg)	2 weeks	-2.1	34%
CR845 (5mg) - Hip	6 weeks	-2.7	39%

[1] Benson, et. al. Treatment of Osteoarthritis with Celecoxib, a Cyclooxygenase-2 Inhibitor: a Randomized Controlled Trial. *Mayo Clin Proc. 1999;74:1095-1105.*

[2] Chappell et. Al., Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-controlled trial. *PAIN.* Volume 146, Issue 3, 5 December 2009, Pages 253–260.

[3] Markenson, et. al., Treatment of Persistent Pain Associated With Osteoarthritis With Controlled-Release Oxycodone Tablets in a Randomized Controlled Clinical Trial. *Clin J Pain* Volume 21, Number 6, November/December 2005.

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Cara: Financial Highlights

As of June 30th, 2017

- **Cash and Marketable Securities** **$112.4M**
- **Net loss – Q2, 2017** **$9.3M**
- **Shares outstanding** **32.5M**

- **Follow-On Offering 3/31/17 - $86M**

Upcoming Projected Clinical/Regulatory Milestones

2H 2017

EoPII FDA Meeting: IV CR845 CKD-aP	Q3, 2017
Initiation Phase 3 IV CR845 CKD-aP	Q4, 2017
Phase 1 Oral CR845 CKD-aP (III-IV)	Q4, 2017
IND/Phase 1 Oral CR845 CLD-aP	Q4, 2017
Complete Enrollment Phase 3 Post-Op	Q4, 2017

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